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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,508	STUART ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *1-43 and 46-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-64 are pending. Claims 1-43 and 46-64, drawn to non-elected claims, are withdrawn from consideration. Claims 44 and 45, to the extent, they read on methods where all three components are measured, are examined on the merits.

Objections/Rejections Withdrawn:

2. The objection to the abstract is withdrawn in view of applicants' arguments.

Objections/Rejections Maintained:

3. The objection to claim 45 for reciting "and/or" is maintained for the reasons of record. Applicants are reminded of the restriction requirement mailed 4/22/2003. Invention group IX, which was elected by applicants, construes the claims to be drawn to methods of detecting gp75, antibodies thereto ***and*** c-erbB-2 ligands. Applicant may file separate applications with claims to cover the non-elected invention groups V, VII and VIII, which also include claims 44 and 55. Correction is required.

4. The rejection of claims 44 and 45 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for the reasons of record.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants maintain that, when read in light of the specification, the scope of the claimed methods is clear. This argument is not persuasive because, for example, the step of "classifying patients as to their chances of long term survival or time to relapse of the disease" assumes that the patients already have a disease. However, the preamble of the claim is in part directed to screening or diagnosing neoplastic disease, which would encompass testing individuals who were not yet known to have a disease. Therefore, the patient population is not clearly set forth, and the scope of the claims is indefinite. The rejection is also maintained because the correlation step is unclear. The claims do not recite a specific relationship between a detected parameter and the accomplishment of any of the stated purposes of the claim. Applicants have not pointed to a specific portion of the specification that could be used to bring clarity to claims.

The rejection of claim 45 is maintained as indefinite because the phrase "the human body fluid" lacks antecedent basis in claim 44. Applicant has not shown where the basis for "the human body fluid" is found in claim 44. Claim 44 is not limited to methods comprising measurements in human body fluids. Amendment of the phrase "*the* human body fluid" to "*a* human body fluid" would overcome this ground of rejection.

5. The rejection of claims 44 and 45 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for the reasons of record.

The basis for this rejection is that the claimed methods are not described in the specification because the methods require the measurement of gp75, antibodies thereto and c-erbB-2 **ligands**, but the specification fails to describe the structure of any c-erbB-2 **ligand**. Therefore, methods for detecting c-erbB-2 **ligands** are not described.

Applicants are reminded that the written description requirement is severable from the enablement requirement under 35 U.S.C. 112, first paragraph.

A review of the specification demonstrates that applicant was not in possession of a c-erbB2 ligand at the time of filing. Therefore, applicant would not have been in possession of any of the tools required for measuring levels of a c-erbB-2 ligand at the time of filing. Furthermore, at the time of filing, applicant had not established any relationship between cancer diagnosis or prognosis and levels of c-erbB-2 ligand. A review of the prior art demonstrates that it was not until September 1990, more than a year after applicants' effective filing date, that one c-erbB-2 ligand, gp30, was in the public domain (Lupu, R. et al. Science 249(4976): 1552-1555, 1990, Sep.). Therefore, the claimed inventions lack adequate written description and applicants were not in possession of the claimed invention at the time of filing.

Applicants' arguments have been considered, but fail to persuade. Applicant appears to be arguing that because the pending claims do not recite cDNA sequences, and because the claims are directed to methods and not to compositions, that the disclosure of a specific ligand is not relevant to the written description issue. This argument is not found persuasive because one must be in possession of the claimed invention at the time of filing. If the specification fails to describe one of the ligands that is to be measured in the claimed methods, and, more importantly, fails to provide any teachings demonstrating that any relationship exits between amounts of this

ligand and neoplastic disease, then applicant has failed to demonstrate possession of the claimed invention at the time of filing. The passages pointed to in applicants' response appear to be prophetic contemplations that a relationship might exist between amounts of c-erbB-2 ligand and neoplastic disease. Therefore, the rejection is maintained.

6. The rejection of claims 44 and 45 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for the reasons of record.

Claims 44 and 45 are drawn to methods for screening for neoplastic disease, disgnosing neoplastic disease, monitoring the disease status of patients with neoplastic disease or prognosticating the course of neoplastic disease, comprising c and quantitating the level of gp75 proteins or polypeptides, antibodies to gp75 and level of ligand to c-erbB-2, correlating the detected levels; and classifying patients as to their chances of long term survival or a time to relapse of the disease. The method may be performed after an operation to remove tumor wherein the presence of gp75 proteins or polypeptides, antibodies to gp75 and level of ligand to c-erbB-2 in a human body fluid is indicative of metastases. The term gp75 appears to refer to the extracellular domain of c-erbB-2.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence

or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The claimed inventions are drawn to methods where three variables are measured and the measurements are used to estimate the chance of a patient's long-term survival of or time to relapse of a neoplastic disease. The specification fails to establish any relationship between any of the three variables and long-term survival of or time to relapse of a neoplastic disease, and fails to establish a relationship between all three of the measured variables.

In the case of gp75, the specification demonstrates an assay for this protein in the sera of breast cancer patients and compares the results to an assay from Centocor. However, this working example is not commensurate in scope with the claims, because the results are not correlated with long term survival or relapse of breast cancer, and the results are not correlated with measurements of antibodies to gp75 or to ligands to c-erbB-2. Therefore, the specification fails to establish any relationship between the purpose of the claimed methods and measurement of gp75 as a single factor, or as part of a three-factor testing system. Furthermore, the scope of the working example, which is an example using breast cancer patients, is not commensurate in scope with the scope of the claims, which are drawn to screening, diagnosing, monitoring, or prognosticating any neoplastic disease.

In the case of gp75 antibodies, there is no data at all in the specification demonstrating that gp75 antibodies are detectable in the sera of any cancer patient. Post-filing date art teaches that antibodies to c-erbB-2 (and presumably some are directed to the extracellular domain of c-erbB-2) may be found in the sera of some cancer patients, but this teaching does not establish

any diagnostic utility for measuring the levels of such antibodies (Disis, M.L. et al. J. Immunology, 156: 3151-3158, 1996; see page 3151, 2nd col.). Therefore, the specification fails to establish any relationship between the purpose of the claimed methods and measurement of gp75 antibodies as a single factor, or as part of a three-factor testing system.

In the case of c-erbB-2 ligands, there is no data at all in the specification demonstrating that c-erbB-2 ligands are detectable in the sera of any cancer patient, and no c-erbB-2 ligand is described in the specification. Therefore, the specification fails to teach even one example for how to measure such ligands. Furthermore, if at the time of filing no c-erbB-2 ligands were known to exist or the functions of such ligands, one of skill in the art would not have known how to relate measurements of the levels of a c-erbB-2 ligand to long term survival or relapse of a neoplastic disease. Post-filing date art teaches that in the case of one c-erbB-2 ligand that was discovered, gp30, that in some circumstances gp30 inhibits tumor growth, and in other cases stimulated cell proliferation (see Lupu, R. et al. Proc. Nat. Acad. Sci. USA, 89(6): 2287-2291, 1992, Abstract only). Therefore, the specification fails to establish any relationship between the purpose of the claimed methods and measurement of c-erbB-2 ligands as a single factor, or as part of a three-factor testing system.

In view of the failure of the specification to establish a relationship between any or all of the factors, and in view of the fact that the specification fails to describe any c-erbB-2 ligand, it would require undue experimentation on the part of a skilled worker to make and use the claimed inventions.

Applicants' arguments have been considered, but fail to persuade. Applicant points to passages in the specification that appear to be a contemplation of the invention to the extent that

gp75 is measured and related to overexpression of c-erbB-2. However, the claims are drawn to methods where three separate measurements are made and all three measurements are used together to diagnose, screen or evaluate neoplastic disease. The specification provides no actual data using all three factors, and one of the factors, the relationship between levels of c-erbB-2 ligand, is not established either in the specification or in the prior art. Furthermore, it is not even known what the chemical structure is of any c-erbB-2 ligand. Therefore, the specification fails to place into the hands of the skilled practitioner the means to measure c-erbB-2 ligand. Furthermore, even if applicant can show that a c-erbB-2 ligand was known at the time of filing, the relationship between levels of this ligand and neoplastic disease are not established, but only contemplated in the specification. Therefore, it appears that the specification offers nothing more than an invitation for further experimentation on the claimed invention itself.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
September 3, 2004

SHEELA HUFF
PRIMARY EXAMINER